A Petition for a two (2) month Extension of [illegible] currently herewith, which extends the period for response from 16 January 200[illegible]3. Because 16 March 2003 falls on a Sunday, the response period is extended to [illegible]ch 2003, pursuant to 37 CFR § 1.7.

Please amend the application as follows:

IN THE SPECIFICATION:

Please amend the specification as set forth in Appendix B.

REMARKS

Claims 1-14 and 17-34 are currently pending. A clean version of the pending claims is submitted herewith as Appendix A.

The specification has been amended, *intra alia,* to correct obvious spelling, trademark, and other typographical errors, as suggested by the Examiner. No new matter has been added by way of this amendment. Other amendments to the specification are discussed in more detail herein, and have been made to place the application in better condition for appeal.

Applicants respectfully request reconsideration of the pending claims 1-14 and 17-34.

Applicants also respectfully request that the Patent Attorney Docket No. be changed from ALX-149 to ALX-20 FWC (109488-128).

I. Objection to Under 35 U.S.C. § 132

The Amendment filed 05 November 2001 (Paper No. 37) stands objected to under 35 U.S.C. § 132 as allegedly introducing new matter into the disclosure. The Examiner objects to the amendments to pages 56, 59 and 60 of the specification for failing "to have adequate written description support in the application as-filed" (Office Action, page 2).

Applicants respectfully traverse this objection.

In the Preliminary Amendment, filed on 05 November 2001, Applicants amended the specification to insert text relating to the ability of the 5G1.1 antibody to bind to both the alpha and beta chains of human C5 protein, as determined by immunoblot assay. After entry of this amendment, the text of Example 8 of the instant application exactly corresponds to the text of Example 7 in Wang *et al.* (U.S. Patent No. 6,074,642 (hereafter the '642 patent), columns 18-19, (submitted previously). The Wang *et al.* application (U.S. Serial No. 08/236,208), which evolved into the '642 patent, was incorporated by reference into the specification of the instant application *in its entirety* (see page 6, lines 6-7 and page 60, lines 11-16).

"The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the application as filed. Replacement of the identified material incorporated by reference with the actual text is not new matter." (M.P.E.P. § 2163.07(b). See also *Mendenhall v. Astec Industries Inc.*, 13 USPQ2d 1913, 1922 (E.D. Tenn. 1988), aff'd, 887 F.2d 1094, 13 U.S.P.Q.2d 1956 (Fed. Cir. 1989) (unpublished) ("A patent application may comply with 35 U.S.C. § 112 by incorporating by reference the disclosure of another pending United States patent application."); *Ernsthausen v. Nakayama*, 1 U.S.P.Q.2d 1539, 1547 (Bd. Pat. App. & Int'f 1985), *aff'd*, 809 F.2d 787 (Fed. Cir.

1986) (unpublished) ("An application for a patent when filed may incorporate essential material by reference to a United States patent"). Therefore, Applicants have not added new matter to the specification by way of the 05 November 2001 Preliminary Amendment, as the added text was identical to text in a patent application, which was properly incorporated by reference in its entirety in the as-filed application.

Thus, contrary to the Examiner's assertions, no new matter was added by way of the 05 November 2001 Preliminary Amendment.

However, solely in order to simplify issues for appeal, Applicants have amended the specification to cancel the second paragraph of the Amendment to page 59-60 of the specification (*see* 05 November 2001 Amendment to Specification; Paper No. 37).

Applicants have retained matter added in the 05 November 2001 amendment to the specification related to the ability of the 5G1.1 antibody to bind to both the alpha and beta chains of C5 as this language merely recites an inherent property of the 5G1.1 antibody, and does not add new matter to the specification.

> By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 U.S.P.Q. 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 U.S.P.Q. 279 (CCPA 1973). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Manual of Patent Examining Procedure, Eighth Edition ("M.P.E.P.") § 2163.07 (a), (emphasis added). *See also Jewish Hospital v. St. Louis v. Idexx Laboratories* (951 F.Supp. 2, 4, 42 U.S.P.Q. 2d 1720, 1723) (D. Maine 1996)

> The original application made clear that the applicant was claiming to have discovered and was seeking a patent for newly-defined antigens in dog blood or sera, new antibodies, and new tests for determining the presence of heartworm. For the antigens, the original claim listed six characteristics. The continuation-in-part added four more. These additional characteristics are inherent in the antigens originally discovered; they simply add more descriptive criteria...Since the continuation-in-part provides inherent characteristics of the items previously disclosed in the 1983 application, it does not result in a later effective date.

(emphasis added); *Kennecott Corp. v. Kyocera Int'l, Inc.,* 835 F.2d 1419, 1421-22 (Fed.Cir.1987) (entitling a description of the inherent property of an "equiaxed microstructure," though later added to the specification, to the original filing date because "anyone with a microscope would see the microstructure of the product."); *In re Nathan,* 328 F.2d 1005, 1009 (later added limitation to the claims that a class of 2-halo steroids had an "alpha orientation" was not new matter because the amendatory material was "concerned with an inherent characteristic of an illustrative product of applicants' invention already sufficiently identified in appellants' original disclosure as filed.").

The inherent property of the 5G1.1 antibody to bind both the alpha and beta chain of C5 is confirmed in the Wang *et al.* '642 patent discussed above. Thus, the inherent property of the 5G1.1 antibody would have been known to one of skill in the art at the time the application was filed. Because the characteristic of the 5G1.1 antibody to bind to both the alpha and beta chains of C5 is inherent in the antibody, it is simply a "more

descriptive criterion" and does not add new matter to the specification. Furthermore, the characteristic of the 5G1.1 antibody to bind to both the alpha and beta chains of C5 "would be so recognized by persons of ordinary skill."

Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

II. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 19-34 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification does not contain written description of the claimed invention and does not reasonably convey to one of skill in the art that Applicants had possession of the claimed invention (Paper No. 44, section 6).

Applicants respectfully traverse this ground of rejection.

The Examiner opines that "generic disclosure" of C5 blockers on pages 56 and 59-60 of the specification does not provide adequate written description support for the antibodies which "bind to the alpha chain of C5." However, Applicants respectfully direct the Examiner's attention to the Amendments to the specification submitted on 05 November 2001 (05 November 2001 Preliminary Amendment, Appendices A-D), which have been previously entered by the Examiner (Paper No. 38, page 2), and the Amendment to the specification filed herewith. Thus, after entry of these amendments,[1] the specification on, *e.g.,* pages 59-60, now reads

[1] For discussion of the Amendments to the specification, please refer to Section I *supra*.

> The supernatant from a hybridoma designated as 5G1.1 tested positive by ELISA and substantially reduced the cell-lysing ability of complement present in normal human blood in the chicken erythrocyte assay. Further analyses revealed that the 5G1.1 antibody has two ~~surprising~~ properties: 1) it reduces the cell-lysing ability of complement present in normal blood so efficiently that, even when present at roughly one-half the molar concentration of human C5 in the hemolytic assay, it can almost completely neutralize serum hemolytic activity; and 2) it binds to both the alpha and beta chains of the human C5 protein.

(emphasis added). Thus, it will be appreciated that there is adequate written support in the specification for antibodies which bind the alpha chain of C5.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. 102(e)

Claims 1-17 have been rejected under 35 U.S.C. § 102(e) over Sims *et al.* (U.S. Patent No. 5,635,178) (Paper No. 44, section 8).

Applicants respectfully traverse this ground of rejection.

The Examiner appears to rely solely on the claims of Sims *et al.* The Examiner opines that Sims *et al.* claims methods and compositions comprising antibodies that specifically bind a component of C5b-9 complex, and that, given that C5b is a component of the C5b-9 complex, the claimed methods of Sims *et al.* read on the instant claimed methods for the treatment of established joint inflammation comprising administering an effective amount of a composition comprising a purified antibody specific against C5 (Paper No. 44, Section 6).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added); *Datascope Corp. v. SMEC, Inc.*, 224 USPQ 694, 698 (D. N.J. 1984), *aff'd in part & rev'd in part*, 776 F.2d 320, 227 USPQ 838 (Fed. Cir. 1985) ("Anticipation cannot be predicated on teachings in a reference that are vague or based on conjecture") (emphasis added). *See also Ex parte Standish*, 10 USPQ2d 1454, 1457 (Bd. Pat. App. & Int'f 1989) ("anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product") (emphasis added).

Respectfully, Sims *et al.* does not teach a method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5. For instance, Sims *et al.* teaches in the "Summary of the Invention" that the composition and methods of the invention are related to

> polypeptides having the ability to act as an inhibitor of complement C5b-9 activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa protein found on the surface of human platelets, a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to inhibit the activity of C5b-9, anti-idiotypic antibodies mimicking the action of the inhibitor proteins or antibodies against C7 or C9 which block the formation of the C5b-9 complex.

Column 3, lines 30-40.

For instance, Sims *et al.* teaches a monospecific rabbit antibody against the purified human erythrocyte 18 kDa protein (α-P18) (Col. 7, lines 36-38). The α-P18 antibody binds to the 18 kDa protein on the erythrocyte membrane and prevents the C5b-9 complex from forming on the platelet surface (Col. 9, line 40).

Further, Sims *et al.* states that

> [a]s used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or suppression of complement mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 inhibitory activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal antibodies to C7 that block membrane binding of the C5b-9, monoclonal antibodies to C9 that block C9 polymerization and insertion into the membrane, monoclonal antibodies that blocks C9 binding to C5b-9, and anti-idiotypic antibodies which inhibit the function of the cell surface molecules in inhibiting C5b-9 activity, especially the Fab fragments of monoclonal antibodies having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only inhibitor proteins of human origin will inhibit human C5b-9.

Column 5, lines 30-51 (emphasis added).

However, nowhere does Sims *et al.* teach antibodies specific against C5. Similarly, nowhere does Sims *et al.* teach a method for the treatment of established joint inflammation comprising administering a composition comprising a purified antibody specific against C5.

Even assuming *arguendo* that the C5 antibodies utilized in the instant invention did somehow fall within the broad, generic claims of Sims *et al.* (which Applicants maintain is not the case), a genus does not invariably anticipate a claim to a species within the genus. *Rohm & Haas Co. v. Dawson Chem. Co.,* 557 F. Supp. 739, 806, 217 USPQ 515 (S.D. Tex. 1983), *rev'd*

on other grounds sub nom. Rohm & Haas Co. v. Crystal Chem Co., 722 F.2d 1556, 220 USPQ 289 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) ("A subsequent species invention, even if unobvious and hence patentable over an earlier generic invention, does not render the generic invention unpatentable and does not require restriction of the literal scope of claims to the generic invention so as to exclude the later species."). *See also, e.g., In re Meyer*, 599 F.2d 1026, 1031-32, 202 USPQ 175 (CCPA 1979) ("The genus, 'Alkaline chlorine or bromine solution,' does not identically disclose or describe, within the meaning of § 102, the species alkali metal hypochlorite, since the genus would include an untold number of species."); *In re Kollmann et al.* (CCPA 1979) 595 F.2d. 48, 201 USPQ 193 (Reference not anticipatory because the reference does not highlight the claimed mixture among the many dozen disclosed); *In re Sivaramakrishnan* (CCPA 1982) 673 F.2d. 1382, 213 USPQ 441 (Reference not anticipatory where one skilled in the art would have to choose judiciously from a genus of possible combinations).

Thus, claims 17-34 are not anticipated by Sims *et al.* Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

IV. Rejection Under 35 U.S.C. 103(a)

Claims 1-14 and 17-34 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sindelar *et al.* (U.S. Patent No. 5,173,499) and/or Sims *et al.* in view of Auda *et al.* (Rheumatol. Int. 10:185-18 (1990)), Wurzner *et al.* (Complement Inflamm. 8:328-40 (1991)) and Montz *et al.* (Cell. Immunol. 127:337-51 (1990)) in further view of Rollins *et al.* (U.S. Patent No. 5,853,722).

This ground of rejection is respectfully traversed.

The Examiner cites Sindelar *et al.* as teaching methods for treating established joint inflammation comprising the administration of an effective amount of a C5 blocker. Sims *et al.* is cited to teach antibodies which specifically bind to a component forming the C5b-9 complex. Auda *et al.* is cited to teach the measurement of complement activation products in patients suffering chronic rheumatic diseases to predict patient clinical status. Auda *et al.* is also cited to teach monitoring C5b-9 levels in patients to provide a more sensitive indicator of patient status. Wurzner *et al.* is cited to teach the inhibition of terminal C components by monoclonal antibodies specific for C5. Montz *et al.* and Wurzner *et al.* are further cited to teach C5 inhibitors, which do not affect the early C components.

The Examiner asserts that one of ordinary skill in the art would have been motivated to modify the teachings of Sindelar *et al.* with the teachings of Auda *et al.*, Montz *et al.* and Wurzner *et al.* to use C5 inhibitory antibodies to inhibit inflammatory joint disease. The Examiner contends that the motivation to combine the references is in the use of analogous compounds to those taught in Sindelar *et al.* for the inhibition of C5 activity with a reasonable expectation of success, although the Examiner does not appear to contend that the asserted motivation may be found within the cited references themselves.

"To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *see also In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against

the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Mayne*, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997) ("When relying on numerous references or a modification of prior art, it is incumbent upon the examiner to identify some suggestion to combine references or make the modification."); *In re Paulsen*, 30 F.3d 1475, 1482, 31 USPQ2d 1671, 1676 (Fed. Cir. 1994) ("In reviewing the Board's obviousness conclusions, we have been guided by the well-settled principles that the claimed invention must be considered as a whole, multiple cited prior art references must suggest the desirability of being combined, and the references must be viewed without the benefit of hindsight afforded by the disclosure") (emphasis added).

Applicants once again respectfully direct the Examiner's attention to the Declaration of Dr. Yi Wang pursuant to 37 C.F.R. § 1.132, which was submitted 12 September 1996. Dr. Wang declares that it was not known that the method claimed in the instant application would be successful in treating established joint inflammation. Indeed, published references taught away from the present invention, *i.e.*, they taught that animals carrying a genetic defect, which caused them to have no C5, still developed established joint inflammation (Wang Declaration, paragraph 4, and references cited therein). As Dr. Wang pointed out in his Declaration, based on the teaching of these prior art references, one skilled in the art would have expected that inhibiting C5 in mice would fail to treat established joint inflammation; thus, it was wholly unexpected that administering antibodies specific against C5 to mice would treat established joint inflammation, as was surprisingly discovered by Dr. Wang and his co-inventors (Wang Declaration, paragraph 4).

The Sindelar *et al.* patent is directed to chemically synthesized non-protein organic compounds, which are substituted dihydrobenzofurans, spirobenzofuran-2(3H)-cycloalkanes, and their open chain intermediates, for the inhibition and/or suppression of immune activity (Sindelar *et al.*, abstract).

The Examiner opines that, even though Sindelar *et al.* is directed to chemical compounds, the reference "clearly teaches the biological effects of C5a, including its role in arthritis...and clearly teach administering inhibitive compounds which ameliorate or prevent detrimental effects caused by the complement system, including C5a for diseases or disorders" (Paper No. 44, Section 10).

However, while it is true that Sindelar *et al.* briefly mentions that C5a has "been implicated" in rheumatoid arthritis (Column 4, lines 49-51 and Column 5, lines 57-59), the reference does not teach or make obvious the claimed invention. *See, e.g., Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (Bd. Pat. App. & Int'f 1992) (prior art which provides only general guidance and is not specific as to the particular form of the claimed invention and how to achieve it does not render the invention unpatentably obvious). Further, Sindelar *et al.* does not provide the requisite motivation to combine any of the references cited by the Examiner.

Sims *et al.* is cited to teach antibodies which specifically bind to a component forming the C5b-9 complex. However, as described in more detail elsewhere herein, Sims *et al.* does not teach antibodies specific for C5 as recited in claims 1-17, or specific for the alpha chain of C5 as recited in claims 18-34.

The Examiner opines that Sims *et al.* teaches targeting diseases, such as rheumatoid arthritis, with C5 antibodies utilized in the claimed invention. In particular, the Examiner points

to Column 14, paragraph 2, "particularly line 28" for his assertion. The passage referred to by the Examiner states that

> Treatment of patients with immune disorders and diseases such as...rheumatoid arthritis...is accomplished by administering an effective amount of a composition containing a C5b-9 inactivator as defined above..."

However, the Sims *et al.* patent defines a "C5b-9 inactivator" as follows:

> "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 inhibitory activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal antibodies to C7 that block membrane binding of the C5b-9, monoclonal antibodies to C9 that block C9 polymerization and insertion into the membrane, monoclonal antibodies that blocks C9 binding to C5b-9, and anti-idiotypic antibodies which inhibit the function of the cell surface molecules in inhibiting C5b-9 activity, especially the Fab fragments of monoclonal antibodies having this activity.

Column 5, lines 34-47 (emphasis added).

Thus, Sindelar *et al.* does not teach or suggest methods for the treatment of established joint inflammation using a composition comprising a purified antibody specific against C5. Also, with respect to claims 19-34, Sindelar *et al.* also does not teach or suggest methods for the treatment of established joint inflammation using a composition comprising a purified antibody, which binds the alpha chain of C5. Further, Sindelar *et al.* does not provide the requisite motivation to combine any of the references cited by the Examiner.

In an attempt to cure the deficiencies of Sindelar *et al.* and Sims *et al.*, the Examiner cites Wurzner *et al.*, which teaches the production of two monoclonal antibodies, allegedly specific for C5.

Wurzner *et al.* does nothing to correct the deficiencies of Sindelar *et al.* or Sims *et al.* As described above, neither Sindelar *et al.* nor Sims *et al.* teaches or suggests methods for the treatment of established joint inflammation using a composition comprising a purified antibody specific against C5. Similarly, Wurzner *et al.* does not teach or suggest, and is not enabling for, the use of antibodies specific against C5 for the treatment of established joint inflammation. Wurzner *et al.* teaches the production of two monoclonal antibodies. Based on *in vitro* testing, these antibodies are stated to be specific for C5. Wurzner *et al.* does not describe any *in vivo* studies to show that the antibodies would be effective *in vivo*, much less effective for the treatment of established joint inflammation, as was shown of the antibodies used in the instant application (see *e.g.*, Examples 1 and 2).

Moreover, the prior art references fail to provide the requisite motivation to substitute the teachings of Sindelar *et al.* or Sims *et al.* with Wurzner's monoclonal antibodies directed against C5. At best, the Wurzner reference only speculates that such C5 antibodies may be useful to arrest the complement cascade, which may be beneficial for some diseases. In fact, while the authors speculate that the C5 antibodies may be useful to arrest the complementary cascade, they fail to teach or suggest the stage at which to arrest the complement cascade to achieve clinical usefulness:

> Arresting the complement cascade at an earlier stage may not be the most clinically useful point to prevent TCC [terminal complement complex] formation because both activation pathways as well as cleavage of C5 by injured tissue-related enzymes...or C5 activation by oxygen radicals...would have to be blocked. Arresting the complement cascade at a later stage, as shown with anti-C8 mabs..., will neither inhibit membrane insertion of the terminal complement complex nor C5a liberation. (Wurzner at 337; citations omitted).

Wurzner's uncertainty and speculation do not provide the requisite motivation to substitute the Wurzner monoclonal antibodies for the Sindelar C5 blockers. Mere conjecture is not the appropriate standard for obviousness. *Datascope Corp. v. SMEC, Inc.*, 224 USPQ 694, 698 (D.N.J. 1984), *aff'd in part & rev'd in part* 776 F.2d 320, 227 USPQ 838 (Fed. Cir. 1985) ("Anticipation cannot be predicated on teachings in a reference that are vague or based on conjecture").

Similarly, Wurzner *et al.*, either alone in combination with Sindelar *et al.* and/or Sims *et al.*, does not anticipate or render obvious claims 19-34, which recite a method for the treatment of established joint inflammation in a patient in need thereof comprising administering a composition comprising a purified antibody, which binds the alpha chain of C5. Specifically, Wurzner *et al.* discusses the production of two monoclonal antibodies, N19-8 and N20-9, which are specific against the beta chain of C5 (see Wurzner *et al.*, page 337, left column, lines 4-6). The specific use of these C5 beta chain-specific antibodies to treat joint inflammation is not taught or suggested. Applicants submit that the effective use of a composition comprising a purified antibody, which binds the alpha chain of C5, in a method for the treatment of established joint inflammation, was not known in, much less suggested by, the prior art including Wurzner *et al.*, and thus that Wurzner *et al.* does not supply the deficiencies of Sindelar *et al.* and/or Sims *et al.* Thus, claims 19-34 also distinguish over Wurzner *et al.*, alone or in combination with any other reference of record.

In a further attempt to cure the deficiencies of Sindelar *et al.* and Sims *et al.*, the Examiner cites Montz *et al.* However, the Montz *et al.* reference does nothing to correct the deficiencies of Sindelar *et al.*, Sims *et al.*, and/or Wurzner *et al.* Montz *et al.* discusses

experiments to determine the potential role of endogenously synthesized C5 and subsequently generated C5a in *in vitro* autologous T cell stimulation. Montz *et al.* is directed to analyzing the inhibitory effect of anti-C5a against autologous T cell proliferative responses *in vitro*. Montz *et al.* does not teach or suggest an *in vivo* method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5. Similarly, Montz *et al.* does not teach or suggest an *in vivo* method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody, which binds the alpha chain of C5, as required by claims 19-34. Therefore, neither Wurzner *et al.* nor Montz teaches or suggests the use of anti-C5 antibodies to treat established joint inflammation in a patient, and thus neither supplies the deficiencies of Sindelar *et al.* or Sims *et al.*, alone or in combination.

The Examiner cites Auda *et al.* which, respectfully, does nothing to remedy the deficiencies of Sindelar *et al.*, Sims *et al.*, Wurzner *et al.*, and Montz *et al.* Auda *et al.* merely describes measuring complement activation products in patients. While it is an interesting fact that C5b-9 complex levels were increased in patients with chronic rheumatic diseases, as discussed above, mouse studies in which C5 was completely absent due to a genetic defect continued to develop established joint inflammation (Wang Declaration). In response, the Examiner asserts that the Declaration is found unpersuasive because Auda *et al.* "clearly indicates the involvement of complement in rheumatoid arthritis and the recruitment of PML." However, in addition to showing that C5b-9 complex levels were elevated in patients with chronic rheumatic diseases, Auda *et al.* also showed that early complement component

complexes (in addition to the late complement component C5b-9 complex) were also increased in patients with chronic rheumatic diseases. In fact, C1s:C1-inh, C3bP and C5b-9 complexes were each elevated in all patients (see entire document).

Moreover, Auda *et al.* makes the merely precatory suggestion that "monitoring the levels of complement activation products may provide additional information and allow predictions of clinical status." Similarly, Auda *et al.* does not suggest use of the alpha chain of C5, as required by claims 19-34. The authors do note that the predictive value of a test utilizing C5b9 has been shown in determining the onset of adult respiratory distress syndrome (which is not a disease of established joint inflammation), which allegedly suggests C5b9 may provide a more sensitive indicator than measurements of CH50, C4a, C3a or C5a" (page 188, right column, second full paragraph). However, once again, there is no indication of which of the many complement components found in elevated levels in the blood or patients with chronic rheumatic diseases is most important. There is similarly no indication of the importance of the alpha chain of C5. There is also not any suggestion in Auda *et al.* that antibodies specific against C5 would be useful in treating patients with established chronic joint inflammation, as required by claims 19-34. Thus, Auda *et al.* does not teach or suggest the claimed method of treating established joint inflammation by administering to a patient either a composition comprising a purified antibody specific against C5, or a composition comprising a purified antibody which binds to the alpha chain of C5. Further, Auda *et al.* does not provide any motivation to combine the references cited by the Examiner.

The Examiner asserts that Rollins *et al.* is added to allegedly provide further teachings and evidence that C5-specific antibodies had the property of inhibiting complement inflammatory conditions in humans at the time the invention was made.

The Sindelar *et al.*, Sims *et al.,* Auda *et al.*, Wurzner *et al.*, and Montz *et al.* references are discussed above. Rollins does not remedy the deficiencies of the combination of Sindelar *et al.* and/or Sims *et al.,* in view of Auda *et al.*, Wurzner *et al.*, and Montz *et al.* Rollins teaches the use of anti-C5 antibodies to block the generation of activated complement components C5a and C5b following extracorporeal circulation during cardiopulmonary bypass. Indeed, Rollins specifically teaches that "[m]ore generally, the invention relates to the use of anti-C5 antibodies in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient" wherein the "anti-C5 antibody is used to reduce at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion resulting from the circulation of the patient's blood through such a conduit" (Rollins, columns 10-11). In contrast, the methods of treating established joint inflammation encompassed by the claimed invention are directed to administering, to a patient, an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5.

Thus, Rollins does not supply the deficiencies of Sindelar *et al.*, Sims *et al.,* Auda *et al.*, Wurzner *et al.*, and Montz *et al.* Further, the motivation to combine the references is lacking, because none of the prior art references suggests the desirability of modification of the references.

It is not sufficient that the prior art *could be* modified to produce the claimed invention. Rather, the modification is non-obvious unless the prior art suggests the desirability thereof. *In re Laskowski*, 10 USPQ2d 1397 (Fed. Cir. 1989). Further, the invention as a whole must be considered when determining obviousness, and it is improper to consider only the obviousness of any substitution or modification. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Indeed, modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "*unless the prior art suggests the desirability of the modification.*" *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (emphasis added).

Applicants respectfully submit that the required motivation to combine the Sindelar *et al.*, and/or Sims *et al.,* Auda *et al.*, Wurzner *et al.*, Montz *et al.*, and Rollins *et al.* references is completely lacking. Not one of these references, either alone or in combination with the other references, discloses or suggests to the ordinarily skilled person the desirability of the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

V. Conclusion

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a two (2) month Extension of Time is filed concurrently herewith, which extends the period for response from 16 January 2003 to 16 March 2003. Because 16 March 2003 falls on a Sunday, the response period is extended to Monday, 17 March 2003, pursuant to 37 CFR § 1.7. The Petition further authorizes the PTO to charge the two month extension fee of $410 to our Deposit Account No. 08-0219.

Applicants believe no other fees are due in connection with this Amendment. However, if there are any other fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,

Tamera M. Pertmer, Ph.D.
Agent for Applicant
Registration No. 47,856

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APPENDIX A

PENDING CLAIMS 1-14 AND 17-34 – CLEAN VERSION

1. A method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5.

2. The method of Claim 1 wherein the composition is administered in an amount effective to inhibit the cell-lysing capability of complement present in a blood-derived fluid of the patient.

3. The method of Claim 2 wherein the blood-derived fluid is serum.

4. The method of Claim 1 wherein the composition is administered in an amount effective to reduce the level of soluble C5b-9 present in a blood-derived fluid of the patient after activation of complement in that fluid.

5. The method of Claim 4 wherein the blood-derived fluid is serum.

6. The method of Claim 1 wherein the composition is administered in an amount effective to reduce the level of C5a present in a blood-derived fluid of the patient after activation of complement in that fluid.

7. The method of Claim 6 wherein the blood-derived fluid is serum.

8. The method of Claim 1 wherein the composition is administered in an amount effective to reduce the cell-lysing ability of complement present in the synovial fluid of an inflamed joint of the patient by at least 10%.

9. The method of Claim1 wherein the composition is administered in an amount effective to reduce the level of soluble C5b-9 present in the synovial fluid of an inflamed joint of the patient by at least 10%.

10. The method of Claim 1 wherein the composition is administered in an amount effective to reduce the level of C5a present in the synovial fluid of an inflamed joint of the patient by at least 10%.

11. The method of Claim 1 comprising the further step, after the administration of the composition, of determining the C5a level and/or the C5b level in the synovial fluid of an inflamed joint of the patient so as to monitor the course of the patient's response to the administration of the composition.

12. The method of Claim 11 wherein the C5a level is determined by an immunoassay or a chemotaxis assay.

13. The method of Claim 11 wherein the C5b level is determined by measuring the level of soluble C5b-9 in the synovial fluid or by measuring the cell-lysing ability of complement present in the synovial fluid.

14. The method of Claim 1 wherein the composition does not interfere with the cleavage of complement component C3 in the patient's serum into C3a and C3b.

17. The method of Claim 1, wherein said antibody is a monoclonal antibody.

18. The method of Claim 18, wherein said monoclonal antibody is 5G1.1 (ATCC Accession No. HB-11625).

19. A method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody, which binds the alpha chain of C5.

20. The method of Claim 19 wherein the composition is administered in an amount effective to inhibit the cell-lysing capability of complement present in a blood-derived fluid of the patient.

21. The method of Claim 20 wherein the blood-derived fluid is serum.

22. The method of Claim 19 wherein the composition is administered in an amount effective to reduce the level of soluble C5b-9 present in a blood-derived fluid of the patient after activation of complement in that fluid.

23. The method of Claim 22 wherein the blood-derived fluid is serum.

24. The method of Claim 19 wherein the composition is administered in an amount effective to reduce the level of C5a present in a blood-derived fluid of the patient after activation of complement in that fluid.

25. The method of Claim 24 wherein the blood-derived fluid is serum.

26. The method of Claim 19 wherein the composition is administered in an amount effective to reduce the cell-lysing ability of complement present in the synovial fluid of an inflamed joint of the patient by at least 10%.

27. The method of Claim19 wherein the composition is administered in an amount effective to reduce the level of soluble C5b-9 present in the synovial fluid of an inflamed joint of the patient by at least 10%.

28. The method of Claim 19 wherein the composition is administered in an amount effective to reduce the level of C5a present in the synovial fluid of an inflamed joint of the patient by at least 10%.

29. The method of Claim 19 comprising the further step, after the administration of the composition, of determining the C5a level and/or the C5b level in the synovial fluid of an inflamed joint of the patient so as to monitor the course of the patient's response to the administration of the composition.

30. The method of Claim 29 wherein the C5a level is determined by an immunoassay or a chemotaxis assay.

31. The method of Claim 29 wherein the C5b level is determined by measuring the level of soluble C5b-9 in the synovial fluid or by measuring the cell-lysing ability of complement present in the synovial fluid.

32. The method of Claim 19 wherein the composition does not interfere with the cleavage of complement component C3 in the patient's serum into C3a and C3b.

33. The method of Claim 19, wherein said antibody is a monoclonal antibody.

34. The method of Claim 33, wherein said monoclonal antibody is 5G1.1 (ATCC Accession No. HB-11625).

APPENDIX B

AMENDMENTS TO SPECIFICATION

Please amend the specification as follows:

On page 1, immediately after the title, please delete the first paragraph, and replace with the following paragraph:

This application is a continuation application of ~~copending~~ application Serial No. 08/311,489, filed on September 23, 1994, abandoned.

On page 43, please delete the paragraph spanning lines 10-21, and replace with the following paragraph:

Mice from each group were sacrificed and all four legs from each mouse were fixed in 10% buffered formalin and decalcified in a solution of 3.1% HCL, 5% formic acid and 7% ammonium chloride. The tissue samples were embedded in paraffin, sectioned at 5 µm and stained with hematoxylin and eosin. For immunofluorescence staining, paws were decalcified in a 0.1M Tris solution containing 10% EDTA and 7.5% PVP for 3 days and frozen in OCT at -80°C. ~~5µm~~ 5 µm sections were then prepared and stained with ~~9FITC~~ FITC conjugated goat anti-mouse IgG, IgA, and

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#2 IgM (Zymed Laboratories, South San Francisco, CA, Catalog No. 65-6411) at a dilution of 1 to 50.

Please replace the paragraph spanning page 52, line 15 – page 53, line 3 with the following paragraph:

At each time point, an aliquot of whole blood was taken, divided into 3 samples, and A) diluted 1:1 in 2% paraformaldehyde in PBS to evaluate platelet and blood cell activation parameters as discussed in the above-referenced U.S. patent application Serial No. 08/217,391; B) centrifuged to remove all cells and plasma diluted 1:1 in ~~Quidel~~ QUIDEL sample preservation solution (Quidel Corporation, San Diego, CA) and stored at -80°C, following which these frozen diluted plasma samples were thawed and used to evaluate C3a and C5b-9 generation (Examples 5 and 6, respectively), and C) centrifuged to remove all cells and undiluted plasma stored at -80°C, following which these frozen plasma samples were thawed and hemolytic assays were performed as described above.

#3

On page 53, please delete the paragraph spanning lines 11-20, and replace with the following paragraph:

The fresh frozen plasma samples that had previously been diluted in ~~Quidel~~ QUIDEL sample preservation solution following CPB circulation (see Example 4) were assayed for the presence of the complement split product C3a by using the ~~Quidel~~ QUIDEL C3a EIA kit (Quidel Corporation, San Diego, CA). These measurements were carried out according to the manufacturer's specifications. C3a released is expressed in ng/well as determined by comparison to a standard curve generated from samples containing known amounts of human C3a.

H 4

On page 54, please delete the paragraph spanning lines 3-10, and replace with the following paragraph:

Fresh frozen plasma samples that had previously been diluted in ~~Quidel~~ QUIDEL sample preservation solution following CPB circulation (see Example 4) were assayed for the presence of terminal human complement complex C5b-9 using the ~~Quidel~~ QUIDEL C5b-9 kit (Quidel Corporation, San Diego, CA). The amount of soluble C5b-9 (sC5b-9) in each sample was determined using the manufacturer's specifications and is expressed in arbitrary absorbance units.

H 5

Please delete the two paragraphs spanning lpage 56, line 19-page 57, line 4, and replace with the following two paragraphs:

A C5 blocker monoclonal antibody suitable for use in the practice of the present invention and having the ~~unique~~ ability to bind to both the alpha and beta chains of the human C5 protein was prepared ~~in accordance with the teachings of Sims, et al., U.S. Pat. No. 5,135,916,~~ as follows.

~~Balb/c~~ BALB/c mice were immunized three times by intraperitoneal injection with human C5 protein (Quidel Corporation, San Diego, CA, Catalog #A403). The first injection contained 100 µg of C5 in a complete Freund's adjuvant emulsion, the second immunization contained ~~100µg~~ 100 µg of C5 protein in an incomplete Freund's adjuvant emulsion, and the third immunization was ~~100µg~~ 100 µg of protein in PBS. The mice were injected at roughly 2 month intervals.

Please delete the paragraph spanning page 58, line 17-page 59, line 18, and replace with the following paragraph:

A 50 µL aliquot of a 2 µg/mL solution of C5 (Quidel Corporation, San Diego, Calif.) in sodium carbonate/bicarbonate buffer, pH 9.5, was incubated overnight at 4°C in each test well of a 96 well plate (~~Nunc-Immuno F96 Polysorp~~ NUNC-IMMUNO F96 POLYSORP, A/S Nunc, Roskilde, Denmark). The wells were then subjected to a wash step. (Each wash step consisted of three washes with TBST.) Next, test wells were blocked with 200 µL of

blocking solution, 1% BSA in TBS (BSA/TBS), for 1 hour at 37°C. After an additional wash step, a 50 µL aliquot of hybridoma supernatant was incubated in each test well for 1 hour at 37°C with a subsequent wash step. As a secondary (detection) antibody, 50 µL of a 1:2000 dilution of horseradish peroxidase (HRP) conjugated goat anti-mouse IgG in BSA/TBS, was incubated in each test well for 1 hour at 37°C, followed by a wash step. Following the manufacturer's procedures, 10 mg of O-phenylenediamine (Sigma Chemical Company, St. Louis, Mo., Catalog No. P-8287) was dissolved in 25 mLs of phosphate-citrate buffer (Sigma Chemical Company, St. Louis, Mo., Catalog No. P-4922), and 50 µL of this substrate solution was added to each well to allow detection of peroxidase activity. Finally, to stop the peroxidase detection reaction, a 50 µL aliquot of 3N hydrochloric acid was added to each well. The presence of antibodies reactive with C5 in the hybridoma supernatants was read out by a spectrophotometric OD determination at 490 nm.

H 7 Cont

On page 59, please delete the two paragraphs spanning pages 59 - page 60 (*see* 05 November 2001 Amendment to Specification; Paper No. 37), and replace with the following paragraph:

The supernatant from a hybridoma designated as 5G1.1 tested positive by ELISA and substantially reduced the cell-lysing ability of complement present in normal human blood in the chicken erythrocyte assay. Further analyses revealed that the

H 8

5G1.1 antibody has two ~~surprising~~ properties: 1) it reduces the cell-lysing ability of complement present in normal blood so efficiently that, even when present at roughly one-half the molar concentration of human C5 in the hemolytic assay, it can almost completely neutralize serum hemolytic activity; and 2) it binds to both the alpha and beta chains of the human C5 protein.

~~The surprising and unanticipated ability of the monoclonal antibody produced by hybridoma 5G1.1 (the 5G1.1 mAb) to bind to both the alpha and beta chains of the human C5 protein was revealed when immunoblot analysis was undertaken to further characterize the 5G1.1 mAb. Human C5 (Quidel Corporation, San Diego, Calif., Catalog No. A403) was subjected to polyacrylamide gel electrophoresis under reducing conditions, transferred to a nitrocellulose membrane, and probed with the 5G1.1 mAb as a purified IgG preparation. Two bands were immunoreactive with the 5G1.1 mAb at apparent molecular weights corresponding to those of the alpha and beta chains of the human C5 protein.~~